

Racial differences in the risk of invasive squamous-cell cervical cancer

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(Received 29 October 1990; accepted in revised form 22 May 1991)

To investigate reasons for the higher rates of invasive squamous-cell cervical carcinoma among Blacks than Whites in the United States, we examined data from a case-control study of cervical cancer conducted in five geographic areas of the US, supplemented by incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program, and hysterectomy prevalence data from the Cancer and Steroid Hormone Study. We observed only minor differences between Blacks and Whites in the magnitude of relative risks associated with a long interval since last Pap smear, multiple sexual partners, cigarette smoking, a higher number of births, and low levels of income and education. Thus, differences in the strength of associations contributed little to the higher incidence rate in Blacks, but the prevalence of these risk factors, except for cigarette smoking, was higher in Blacks than Whites. The SEER incidence rate ratio of 2.3 for Blacks compared to whites was increased to 2.7 when incidence rates utilized denominators corrected for prevalence of hysterectomy, while the rate difference increased from 14.9 to 25.8 cases per 100,000 person-years (PY). We estimated further that, after adjustment for prevalence of hysterectomy, the incidence rate for women at the lowest levels of exposure to the risk factors evaluated was 2.2 times higher in Blacks than Whites, but that the corresponding rate difference was only 2.2 cases per 100,000 PYs. Thus, our results suggest that racial differences in the prevalence of exposure to identified risk factors account for most of the difference in incidence rates. It remains to be determined what, as yet unidentified, aspects of lower socioeconomic status contribute to the higher incidence rate in Blacks.

Key words: Blacks, cancer, cervix, race, United States, Whites.

Introduction

Incidence rates for invasive cervical cancer in the United States are approximately twice as high in Blacks as Whites. This difference is more pronounced for squamous-cell and adenosquamous carcinomas than for adenocarcinomas, has persisted over time and, at least until recently, has been evident at all ages of diagnosis.^{1,2}

Although the causes of cervical cancer are uncertain, a number of risk factors have been identified, in studies primarily of Whites. These risk factors include: having

multiple sexual partners; early age at first sexual intercourse; cigarette smoking; low socioeconomic status; failure to receive regular Pap smears; and a history of sexually transmitted diseases—particularly human papillomavirus (HPV) infection.^{3,4} Possible explanations for the racial disparity in incidence include differences in the relative impact or the prevalence of known risk factors, differences in the prevalence of hysterectomy involving removal of the cervix, and effects of unidentified or unmeasured risk factors.

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To evaluate these possibilities, we examined previously unpublished race-specific data from a case-control study of cervical cancer conducted in several areas of the US, supplemented by incidence data from the Surveillance, Epidemiology, and End Results (SEER) Program,⁵ and hysterectomy prevalence data from the Cancer and Steroid Hormone (CASH) study.⁶

Methods

The case-control study was conducted in five areas reporting to the Comprehensive Cancer Patient Data System—Birmingham (Alabama), Chicago (Illinois), Denver (Colorado), Miami (Florida), and Philadelphia (Pennsylvania).⁷ Women aged 20 to 74, diagnosed as having invasive cervical cancer from April 1982 to January 1984, at 24 participating hospitals, were included in the study. Two controls, individually matched to each case on telephone exchange, race (Black, White, Hispanic, other) and five-year age group, were identified through random-digit dialing techniques.^{8,9} Home interviews were obtained for 73 percent (277) of eligible White cases, 74 percent (157) of Black cases, 74 percent (507) of White controls, and 69 percent (236) of Black controls. The major reason for nonresponse among both cases and controls was refusal (10 percent of cases and approximately 22 percent of controls, among both Blacks and Whites). Other reasons for nonresponse included subjects having moved or not being located, death, and illness.

Analyses were restricted to the 87 percent of cases with invasive squamous-cell cervical carcinoma, other specified carcinomas, and carcinomas not otherwise specified (ICD-O codes 8010-8130),¹⁰ hereafter called squamous-cell carcinomas. We excluded adenocarcinomas and adenosquamous carcinomas (ICD-O codes 8140-8570), which have somewhat different risk factors¹¹ and are too rare for examination by race in our study. Analyses were also restricted to non-Hispanics (92 percent of all cases). Thus, the case-control analysis included 212 White and 127 Black cases with invasive squamous-cell carcinoma, and 484 White and 214 Black controls.

The relative risk (RR), as estimated by the odds ratio (OR), was used to evaluate effects of exposures on cervical cancer risk using data from the case-control study. Both conditional and unconditional logistic regression analyses were performed to obtain ORs and 95 percent confidence intervals (CI), and to test for the statistical significance of interactions.¹² Tests for trend in the logistic analyses were obtained by categorizing the exposure variable, assigning the score 'j' to the jth exposure level of the categorical variable, and treating

the scored variable as continuous. In the unconditional analyses, residential zip codes were used as a proxy for telephone exchange—one of the matching factors—because zip codes were easier to define geographically than telephone exchanges. For each of the five study centers, subjects were grouped into: (i) those living in the central city or metropolitan area, and (ii) those living farther away. Finer stratification on the basis of zip codes did not alter results appreciably. Conclusions based on the conditional analyses were similar to those from the unconditional analyses; the latter were chosen for presentation to allow inclusion of more study subjects.

Population attributable risks among Blacks and Whites were calculated according to the method of Bruzzi *et al.*¹³ This method is based upon the distribution of exposure among the cases only and assumes they are a random sample of cases. Because many of the risk factors for cervical cancer do not have a natural baseline category, women with the lowest level of exposure were considered 'nonexposed.' Calculations of summary attributable risks for all risk factors acting together were based upon the number of cases in each of the strata obtained by cross-classifying the risk factors and RRs obtained from the regression model, assuming no interactions among the risk factors.

To supplement results from the case-control study, we examined incidence data from the four areas of the SEER Program with sizable numbers of Blacks and Whites: Atlanta (Georgia); the State of Connecticut; Detroit (Michigan); and San Francisco-Oakland (California).⁵ Analyses included all invasive squamous-cell cervical carcinomas, as defined above.

Incidence rates were adjusted for prevalence of hysterectomy by reducing the population at risk according to race- and age-specific hysterectomy rates. For women aged 20-54 years, the prevalence of hysterectomy was estimated by five-year age group from data obtained from controls included in the Atlanta, Connecticut, Detroit, and San Francisco-Oakland centers of the CASH study, which was limited to women under the age of 55 years.⁶ For women aged 55 years and older, prevalence rates from the CASH study for women aged 50-54 years were used. This decision was based on 1980 discharge data from short-stay non-Federal hospitals which indicated that the proportion of women with intact uteri remained fairly constant after the age of 50 years.¹⁴ All analyses based on SEER data were limited to the years 1978-84 because they closely surround 1981, the year the CASH study was conducted.

Baseline incidence rates among subjects at the lowest levels of identified risk factors were computed for Blacks and Whites as the product of the SEER inci-

Table 1. Risk factors for invasive squamous-cell cervical carcinoma, by race

	Blacks			Whites		
	Cases	Controls	RR ^a	Cases	Controls	RR ^a
Interval since last Pap (years)						
< 2	51	147	1.0	90	347	1.0
2-9	33	40	2.4	73	104	2.8
≥ 10	13	6	5.0	28	16	7.2
Never	30	21	5.9	21	17	6.3
Trend test			$P < 0.01$			$P < 0.01$
Number of sexual partners						
0-1	14	30	1.0	55	232	1.0
2-4	50	83	1.8	83	163	1.7
≥ 5	63	101	2.6	74	89	3.8
Trend test			$P = 0.05$			$P < 0.01$
Age at first intercourse (years)						
Never or ≥ 19	23	49	1.0	78	286	1.0
17-18	45	66	1.3	76	125	1.6
< 17	59	99	0.6	58	73	1.6
Trend test			$P = 0.13$			$P = 0.12$

^a Adjusted for age (< 35, 35-44, 45-54, > 54), area, and other risk factors in Tables 1-2.

dence rate, both unadjusted and adjusted for prevalence of hysterectomy, times the quantity '1' minus the summary attributable risk, which was derived from the case-control study.¹⁵ These baseline incidence rates were used to estimate the disparity in incidence between Blacks and Whites in the absence of exposure to the identified risk factors.

Results

The risk factors for invasive squamous-cell carcinoma by race based on our case-control study are presented in Tables 1 and 2. All RRs were adjusted for the other risk factors, as well as for area and age. A long interval since last Pap smear significantly increased risk in both racial groups. Relative to having a Pap smear within the previous two years, the risks associated with 10 or more years since last Pap smear were 5.0 in Blacks and 7.2 in Whites. The corresponding RRs among those never having a Pap smear were 5.9 in Blacks and 6.3 in Whites. In both races, the risk rose with increasing number of sexual partners, with the RRs associated with five or more sexual partners compared to none or one partner, being 2.6 in Blacks and 3.8 in Whites. There was no clear trend in risk with age at first intercourse among Blacks, whereas, among Whites, the RR was 1.6 for those with age at first intercourse less than 17 years compared with no intercourse or first intercourse after age 18.

Relative to nulliparous women, risk increased with number of births, reaching 3.3 in Black women and 1.7 in White women for four or more births. Smokers were at increased risk compared to nonsmokers in both races, although a trend with increasing intensity of smoking was clearest in Blacks. Education was related inversely to risk among both Blacks and Whites, with those who had not graduated from high school having twice the risk of those with at least one year of college. The RR associated with a household income of less than or equal to \$10,000, compared to an income of greater than \$20,000, was 1.3 in Blacks and 1.9 in Whites.

None of the trends in RR differed significantly between Blacks and Whites except for those associated with age at first intercourse (the P -value for the interaction term in the logistic model was 0.02).

To estimate how much of the higher incidence in Blacks reflected greater exposure to these risk factors, we examined the proportion exposed among Black and White controls in our study (Table 3). Similar percentages of Blacks and Whites did not have a Pap smear within the previous two years (30 percent and 29 percent respectively). Considerably higher proportions of Blacks than Whites reported two or more sexual partners (86 percent *cf* 51 percent) and first intercourse before the age of 19 (78 percent *cf* 40 percent). A higher proportion of Blacks than Whites also reported one or more births (90 percent *cf* 81 percent). A slightly

Table 2. Risk factors for invasive squamous-cell cervical carcinoma, by race

	Blacks			Whites		
	Cases	Controls	RR ^a	Cases	Controls	RR ^a
Number of births						
0	8	21	1.0	31	96	1.0
1-3	44	111	1.3	123	311	1.3
≥ 4	75	82	3.3	58	77	1.7
Trend test			$P < 0.01$			$P = 0.12$
Cigarettes/day						
Nonsmoker	57	115	1.0	65	242	1.0
< 10	9	27	0.8	13	27	1.6
10-39	54	66	2.3	103	186	1.4
> 39	7	6	4.1	31	29	1.6
Trend test			$P < 0.01$			$P = 0.05$
Education (years)						
> 12	21	64	1.0	62	227	1.0
12	24	65	0.8	73	176	1.3
< 12	82	85	2.0	77	81	2.0
Trend test			$P = 0.04$			$P = 0.02$
Income (\$)						
> 20,000	19	45	1.0	91	288	1.0
10,001-20,000	16	68	0.4	51	130	1.0
≤ 10,000	92	101	1.3	70	66	1.9
Trend test			$P = 0.26$			$P = 0.04$

^a Adjusted for age (< 35, 35-44, 45-54, > 54), area, and other risk factors in Tables 1-2.

Table 3. Percentages^a of Black and White controls according to cervical cancer risk factors

Risk factor	Blacks (%)	Whites (%)
Interval since last pap smear		
< 2	70	71
≥ 2	30	29
Number of sexual partners		
0-1	14	49
> 1	86	51
Age at first intercourse		
≥ 19	22	60
< 19	78	40
Number of births		
0	10	19
≥ 1	90	81
Smoking status		
Nonsmoker	54	50
Smoker	46	50
Education (years)		
Graduated high school	62	83
Not graduated high school	38	17
Annual household income		
> \$20,000	22	60
≤ \$20,000	78	40

^a Percentages are age-adjusted.

higher percentage of Whites, however, reported ever having smoked for six months or longer. Socioeconomic status was clearly related to race, with considerably higher proportions of Blacks than Whites having not graduated from high school (38 percent cf 17 percent), or having incomes less than or equal to \$20,000 per year (78 percent cf 40 percent).

Attributable risks for the major risk factors according to race are shown in Table 4. RRs from the combined group of Blacks and Whites were used in the calculation of attributable risk. The model included age, area, all major risk factors, and an interaction term between age at first intercourse and race. Therefore, racial differences in attributable risk for all factors other than age at first intercourse reflect differences in the prevalence of exposure. Not having a Pap smear within the previous two years contributed substantially to disease in both Blacks and Whites (42 percent cf 40 percent). Also substantial, was the attributable risk associated with having two or more sexual partners (42 percent and 35 percent in Blacks and Whites, respectively). Not having a high school education was associated with considerably more disease in Blacks than Whites (34 percent cf 19 percent). The risk attributable to smoking was slightly lower in Blacks than Whites (23 percent cf 29 percent), while the risk

Table 4. Risk attributable to the major cervical cancer risk factors, by race

	RR ^a	Blacks		Whites	
		Cases exposed (%)	AR (%)	Cases exposed (%)	AR (%)
Two or more years since last Pap smear or never had a Pap smear	3.3	60	42	58	40
Two or more sexual partners	1.9	89	42	74	35
Not graduated from high school (%)	2.1	65	34	36	19
Ever smoked	1.7	55	23	69	29
Parous	1.3	94	22	85	20
Age at first intercourse < 19 years	1.2 (B) 1.8 (W)	82	14	63	28
Household income ≤ \$20,000	1.2	85	14	57	10
Total			90		87

^a Relative risk for Blacks and Whites combined, adjusted for age, area, and other risk factors.

due to parity was about 20 percent in each group. First intercourse before the age of 19 contributed to 14 percent of disease in Blacks and 28 percent in Whites, due to the higher RR in Whites. The risk attributable to having an annual household income of less than or equal to \$20,000 was small in both Blacks and Whites (14 percent of 10 percent). Overall, approximately 90 percent of disease in Blacks of 87 percent in Whites was attributable to these factors.

Based on SEER data from four registries, the population-based incidence rate of invasive squamous-cell

cervical carcinoma was 2.3 times higher in Black women compared to White women, reflecting a rate difference of 14.9 cases per 100,000 PYs (Table 5). Among Whites in the CASH study, 619 of 2,634 (24 percent) reported having had a hysterectomy, compared with 141 of 451 (31 percent) of the Black subjects. Thus, adjustment for prevalence of hysterectomy increased the incidence rate ratio to 2.7 and the rate difference to 25.8 cases per 100,000 person-years.

Combining the data from the case-control study and the SEER program, we estimated the incidence rate of squamous-cell cervical carcinoma by race for subjects unexposed to the major cervical-cancer risk factors (i.e., those who were nonsmokers; high school graduates with annual household incomes of \$20,000 or more; nulliparous; with none or one sexual partner and first intercourse at age 19 or older; and having a Pap smear within the previous two years) (Table 5). For Blacks, this estimate was $26.0 \times (1-0.90) = 2.6$ per 100,000 PYs while for Whites it was $11.1 \times (1-0.87) = 1.4$ per 100,000. The Black/White ratio of these rates was 1.9 and the difference was 1.2 cases/100,000. Additional adjustment for the prevalence of hysterectomy yielded estimates of the incidence in those unexposed of $40.6 \times (1-0.90) = 4.1$ cases per 100,000 PYs for Blacks and $14.8 \times (1-0.87) = 1.9$ cases per 100,000 for Whites. The corresponding Black/White rate ratio was 2.2 and the rate difference was 2.2 cases per 100,000 PYs.

Table 5. Incidence rates^a of invasive squamous-cell carcinoma, for blacks and whites aged 20-85+, SEER^b

	Blacks (No. cases)	Whites (No. cases)	Ratio (B/W)	Difference ^a (B-W)
Observed rates				
Unadjusted	26.0 (1,105)	11.1 (2,917)	2.3	14.9
Adjusted ^c	40.6	14.8	2.7	25.8
Estimated rates in unexposed				
Unadjusted	2.6	1.4	1.9	1.2
Adjusted ^c	4.1	1.9	2.2	2.2

^a Per 100,000 person-years; age-adjusted using the 1980 US standard.

^b Based on 1978-84 data from the Atlanta, Connecticut, Detroit, and San Francisco-Oakland centers.

^c For prior hysterectomy based on data from the CASH study⁴.

Discussion

Our results suggest that differences in the magnitude of RRs for many factors, including interval since last Pap smear, number of sexual partners, cigarette smoking, parity, and lower socioeconomic status, contributed little to the higher incidence rates in Blacks. In fact, the RRs associated with early age at first intercourse were higher in Whites than Blacks. By contrast, the prevalence of the established risk factors, except for cigarette smoking, was higher among Blacks than Whites included in our case-control study. These estimates of prevalence are generally consistent with other data sources available. For instance, according to the 1980 US Census,¹⁶ Blacks had a lower median household income than Whites (\$10,943 *cf* \$17,680), and a lower percentage of Blacks than Whites were high school graduates (52 percent *cf* 68 percent, respectively). The Alcohol and Health Practices Survey,¹⁷ conducted in 1983, showed that a higher percentage of Blacks than Whites were never smokers (48 percent *cf* 44 percent). Contrary to our results, however, data from the National Health Survey for 1982 showed that 70 percent of Black females aged 17 and older *cf* 60 percent of Whites, reported having a Pap smear in the two years prior to the interview.¹⁸ In 1973, however, a higher percentage of White than Black women aged 40 years of age and older had a Pap test within two years, compared to approximately equal percentages of Blacks and Whites aged 20-39 years.¹⁹ Thus, despite improvements over time in the screening of Blacks relative to Whites, earlier patterns of screening probably influenced the 1978-84 race-specific incidence rates of cervical cancer.

Based on population-based statistics for the SEER program for 1978-84, the Black/White incidence rate ratio for invasive squamous-cell cervical cancer was 2.3. More accurate estimation of the populations at risk of developing cervical cancer by adjusting for racial differences in the prevalence of hysterectomy increased the rate ratio to 2.7, indicating that racial differences in the prevalence of hysterectomy mask an even greater disparity in incidence rates.

According to our estimates of attributable risk, the factors examined in this study account for most invasive squamous-cell cervical cancer in both Blacks and Whites, with a slightly higher percentage of disease explained in Blacks than Whites (90 percent *cf* 87 percent). Estimates of incidence rates in those at low levels of identified risk factors, and adjusted for racial differences in the prevalence of hysterectomy, suggest that the rate among Blacks remains twice as high as the rate among Whites, but the rate difference is only 2.2 cases per 100,000 person-years.

Devesa and Diamond²⁰ found that the RR of cervical cancer among Black women relative to Whites in the 1969-71 Third National Cancer Survey was reduced from 1.74 to 1.27 after socioeconomic adjustment based on income, although the rates remained significantly different. In addition, McWhorter *et al*²¹ reported that poverty accounted for nearly all of the racial difference in incidence rates of cervical cancer based on 1978-82 SEER data. More recently, Baquet *et al*²² reported that the disproportionate distribution of Blacks at lower socioeconomic levels accounted for a significant proportion of the excess of cervical cancer in Blacks based on 1978-82 SEER data.

Thus, our findings as well as others' suggest that variations in socioeconomic status and associated risk factors account for much of the racial disparity in incidence of invasive squamous-cell cervical cancer. In addition to the established exposures evaluated in our study, other factors related to socioeconomic status may contribute to racial differences in the incidence of invasive squamous-cell cervical cancer. One possibility is that Blacks have poorer follow-up of positive Pap smears than Whites. In fact, the 1987 National Health Interview Survey indicated that a lower percentage of Blacks than Whites with a positive Pap smear received additional tests, surgery, or other treatment.²³ In addition, several micronutrients, including vitamin A, β -carotene, vitamin C, and folate, have been suggested to reduce the risk of cervical cancer.^{24,25} However, our case-control study revealed no reduced risk of invasive cervical cancer associated with intake of these micronutrients among White women.²⁶ Further evidence that dietary insufficiency probably does not contribute much to the higher incidence among Blacks derived from findings that Black controls in our study consumed on average more vitamin A, carotenoids, vitamin C, and folate than did White controls. These findings are consistent with a recent study in Texas²⁷ and with the 1977-78 US Department of Agriculture Food Consumption Survey,²⁸ which reported that Black women consumed on average more vitamins A and C than Whites. Other potential risk factors that may contribute to differences in cervical cancer occurrence include HPV infection^{3,4} and the sexual behavior of the male partner;²⁹ however, we did not have information on these factors and were therefore unable to assess their likely impact.

One concern in interpreting the results of our case-control study is that it was not population-based. The level of income among White controls in our study was somewhat higher than the US White population, but was more comparable among our Black controls.¹⁶ Because several risk factors were associated with income in our study, it is possible that the summary

and individual attributable risks are underestimates in Whites. This would result in an overestimate of the incidence rate in nonexposed Whites and an underestimate of the Black/White differences in nonexposed. Several other methodologic issues should also be considered. Response rates in our case-control study were less than desirable, but did not differ appreciably by race. In addition, many of the cervical cancer risk factors do not have a natural baseline category, making the calculation of attributable risks somewhat arbitrary. Because most women were exposed to at least one cervical cancer risk factor, our calculations of incidence rates in those without identified risk factors were highly dependent on statistical modeling. Further, in the SEER areas from which incidence rates were derived, Hispanics, whose rates of cervical cancer resemble those of Blacks, could not be distinguished from non-Hispanics.⁵ Finally, we could not evaluate with the CASH data whether the percentage of hysterectomies involving removal of the cervix differed in Blacks and Whites. Thus, our adjustments in the populations at risk of developing cervical cancer may be excessive in one race compared to the other.

In summary, our findings suggest that most of the difference between Black and White cervical cancer incidence rates can be attributed to the disproportionate number of Blacks at lower socioeconomic levels and to a constellation of associated risk factors. Further research is needed to elucidate causal factors and mechanisms and to develop preventive strategies that can be targeted to high risk populations.

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